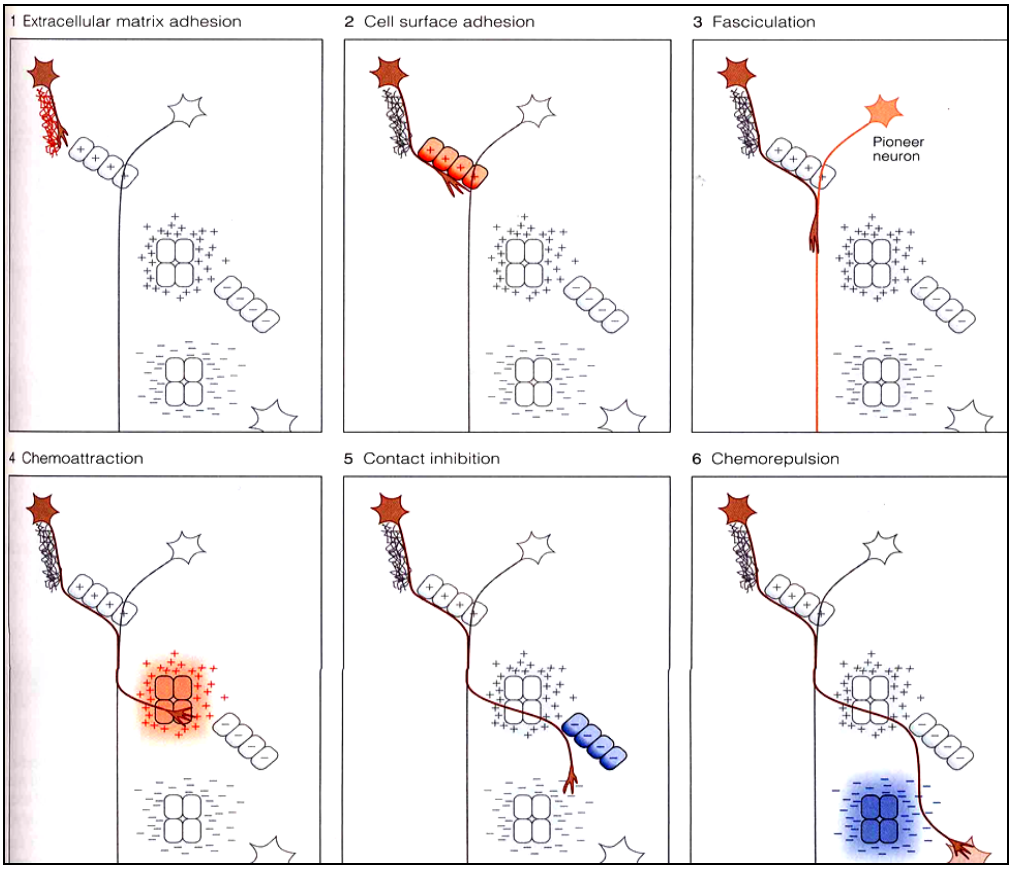
Unit VIII – Problem 10 – Physiology: Integration of Central Nervous System

- **There are 3 overlapping functions in the central nervous system (CNS):**
  - There is a sensory input which will be detected by receptors.
  - Then, sensory input will be explained/ integrated.
  - Eventually, a response will be initiated (representing the motor function).
- **There are 3 level of motor control in CNS:**
  - **The highest level is: pre-motor area and the basal nuclei** (which are responsible mainly for programming).
  - **The motor cortex (primary motor cortex) + cerebellum**: which will decide which muscles must contract, which muscles must relax, the muscle tone, coordination of movement… etc (notice that all of these actions are needed to achieve the desired movement which was chosen by the basal nuclei).
  - **Brainstem and spinal cord**: these are responsible for execution (by affecting the α-motor neurons: lower motor neurons).

  Example (penalty shoot):
  - ✓ The idea of movement for this shoot will be received by the premotor area and basal nuclei (this idea is coming from pre-frontal cortex).
  - ✓ Basal nuclei will chose one of these multiple programs for the movement (the most appropriate one).
  - ✓ The football player will also receive sensory information about the external environment (where is he standing, the wind, where is the goal, where is the goalkeeper… etc). Therefore, he will decide where to shoot.
  - ✓ Primary motor cortex will initiate the movement → the cerebellum will coordinate it and predict the future (telling the player when he is going to reach the football).
- **CNS has synapses which are required for integration of information (synapses are considered as sites of manipulation of information).**
  - **Synapses can be present as:**
    - ✓ Axo-dendritic synapse.
    - ✓ Axo-somatic synapse.
    - ✓ Axo-axonic synapse.
  - So, the synapse is the junction between pre-synaptic and post-synaptic neurons.
  - Synapses were discovered by Loewi who also said that there is a release of neurotransmitters in these synapses (the idea came to him in a dream ☺!!).
  - **There are 2 main types of synapses:**
    - ✓ Electrical synapse: which is characterized by gap junctions and is highly synchronized. This type is represented in control of breathing or in a very synchronized rapid movement such as blinking.
    - ✓ Chemical synapse: which is characterized by a wide synaptic cleft and is composed of 2 elements (pre and post synaptic elements).
      - ❖ Remember that Ca^{++} is the ion which is causing the release of neurotransmitters from storage vesicle by exocytosis.
- **Difference between action potential and synaptic potential:**
  - **Synaptic potential is**: local, graded, summated. Synaptic potential can also be negative/ inhibitory (IPSP) or positive/ excitatory (EPSP).
    - ✓ Inhibition is the result of increased negativity inside the cell by opening of Cl-channels or K-channels.
  - **Action potential is**: not summated.
- **Synaptic vesicle cycle:**
  - The synaptic vesicle is synthesized in endosomes which are present in synaptic terminals. Why are they synthesized in synaptic terminals instead of cell body?

Because even repeated stimulation will not terminate/stop the neurotransmitter release.

- **There are 3 criteria for a neurotransmitter:**
  - It is present in the presynaptic terminal.
  - It is released from storage vesicle by Ca^{++}/ depolarization.
  - It must have a receptor on the postsynaptic membrane.
- **The neurotransmitter is removed rapidly after it is released (Why?) → so the action does not persist for a long time. This removal is done by:**
  - Reuptake.
  - Enzymatic destruction.
  - Diffusion into blood.
- **The neurotransmitter is classified chemically and functionally:**
  - **Chemically.**
  - **Functionally (excitatory or inhibitory):** further classified into:
    - ✓ Direct ionotropic: there is opening of ion channels – for fast transmission.
    - ✓ Indirect metabotropic: there is a second messenger system – for slow transmission.
- **Synaptic integration:**
  - One synaptic potential is summated to the other (each synaptic potential might be excitatory or inhibitory) → if they cause the resting membrane potential of the postsynaptic neuron to reach the threshold → action potential will be generated.
- **Channels:**
  - **Ligand-gated ion channel**: they depend on neurotransmitters which cause them to open (example: Ach binding to a receptor to cause opening of Na-channels and thus influx of sodium ions).
  - **Voltage-gated channels**: which are independent of neurotransmitter (instead, they are depending on the difference in resting membrane potential).
- **GABA receptors are inhibitory. They cause opening of Cl-channels → leading to influx of chloride and resulting in hyperpolarization.**
  - **Notice that chloride is less extracellularly during uterine life. In this condition, GABA will lead to efflux of chloride ions resulting in depolarization (so we cannot say that GABA is always inhibitory).**
- The highest number of neurons is found in the 2nd trimester (which is even exceeding the normal number of neurons to reach more than 100 billion!). As the brain further develops, the number of neurons will increase to reach 200 billion! During the first 2 years of life, the number of neurons will decrease due to development of pathways and centers. At 20 years of age, we will start losing neurons daily (10,000 neurons/day!!).
- **The target of neurons is to reach muscles (notice that targets will secrete NGF so neurons can reach them)**. Example: at birth, there might be 20 neurons which want to innervate a finger that needs only 5 neurons → therefore, the rest of neurons (15 neurons) are going to die. This example tells us that the number of targets in our body is less than the number of neurons.
- **Autistic children have accelerated growth of neurons** (there is no programmed cell death!) → thus they will have a huge number of neurons and axons.
- **Notice that brain growth is a balance between genesis and destruction of cells**. FMR1 gene is inhibiting the protein synthesis in neurons.
- **For neurons to reach their targets, there must be:**
  - Pathway selection.
  - Target selection.
  - Address selection.
- **Different types of axon guidance cues (see the image in next page).**



- **When oligodendrocytes (which are present in the CNS) die** → they release NOGO → which prevents regeneration of neurons. In contrast, **when Schwann cells (which are present in PNS) die** → they don't release NOGO → therefore, regeneration can occur.
  - **If there is an injury in the spinal cord, anti-NOGO injection at the site of injury can be useful and might enhance the process of regeneration.**
- **There are small (neurotransmitters) and big (neuropeptides).**
  - Neuropeptides cannot be synthesized in synaptic terminals or retaken due to their huge size (they are synthesized in cell bodies). In addition, neuropeptides have decreased concentration, increased duration of effect and acting by a second messenger system. Notice that exocytosis of large vesicle containing neuropeptides depends on a general elevation of intracellular calcium.
- **Acetylcholine is secreted from:**
  - Pedunculopontine tegmental nucleus.
  - Basal forebrain complex.
  - laterodorsal tegmental nucleus